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One-year results of a durable polymer everolimus-eluting stent in *de novo* coronary narrowings (The SPIRIT FIRST Trial)

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KEYWORDS

Coronary artery disease, eluting-stent, everolimus, randomized trial.

Abstract

Aim: Short-term results of durable polymer everolimus-eluting stents have shown significant improvements in clinical and angiographic outcomes. This report presents the 1-year clinical and angiographic data from the SPIRIT FIRST Trial.

Methods and results: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus and a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Of the 60 patients enrolled, a total of 56 patients (27 everolimus arm and 29 bare stent arm) were qualified to per-treatment analyses at 1 year. Quantitative angiographic and intravascular ultrasound (IVUS) analyses were performed. Angiographic late loss, IVUS neointimal volume obstruction and major adverse cardiac events (MACE) at 1 year were assessed as the study endpoints. At 1 year, the in-stent late loss and diameter stenosis of patients were 0.24 mm and 18% in the everolimus arm (n=20), as compared with 0.84 mm and 37% in the bare stent arm (n=25, $p < 0.001$). Significantly less neointimal hyperplasia was observed in the everolimus arm compared to the bare stent arm (neointimal volume, 13±9 mm^3 vs. 37±17 mm^3, $p < 0.001$; volume obstruction, 10±7% vs. 28±12%, $p < 0.001$). The overall MACE rate was 15.4% in the everolimus arm and 21.4% in the bare stent arm.

Conclusion: The safety and efficacy of everolimus-eluting stent with a durable polymer observed at 6 months was sustained at 1 year.

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Introduction

To date perculaneous coronary intervention (PCI) using drug-eluting stents is considered the most secure treatment option for *de novo* single coronary artery disease. The two clinically available stents coated with an anti-proliferative drug, sirolimus or paclitaxel, have shown promising clinical and angiographic outcomes as proven in several randomized trials[1-3]. Beside these two drugs, the efficacy of newly developed antiproliferative drugs has been clinically investigated[4-9] and their potent effects in preventing restenosis have been reported[5-9].

Everolimus is a powerful anti-proliferative agent and has shown effect in preventing rejection in kidney and heart transplantation[10-12]. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of DNA synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian Target Of Rapamycin), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with the function of FRAP.

The SPIRIT FIRST clinical trial represents the first evaluation of the everolimus-eluting stent which studied the potential benefits of the local application of everolimus in a durable polymer in combination with a stent with a thin strut design[5]. Compared to identical bare metal stents, everolimus-eluting stents have demonstrated effective suppression of neointimal growth at 6 months[5]. This paper presents the 1-year clinical and angiographic/intravascular ultrasound (IVUS) follow-up results from the experience with the durable polymer everolimus-eluting stent.

Methods

Study population

The SPIRIT FIRST clinical trial was a prospective, controlled, randomized, single-blinded, parallel 2-arm, multicentre clinical evaluation of a durable polymer everolimus-eluting stent (XIENCE™ V, Guidant, Santa Clara, CA, USA) in patients with *de novo* native coronary artery lesions. Patient eligibility criteria, device description and study procedure were previously reported, along with 6-month clinical, angiographic and IVUS analyses[5]. Briefly, study patients had single *de novo* stenoses of < 18 mm lesion length, coverable by 1 study stent, > 50% diameter stenosis, and vessel reference diameter 3.0 mm as assessed by on-line quantitative coronary angiography (QCA). Patients were ineligible if they had any of the followings: evolving myocardial infarction; stenosis of an unprotected left main coronary artery, an ostial location, or located within 2 mm of a bifurcation; a lesion with moderate to heavy calcification, or an angiographically visible thrombus; a left ventricular ejection fraction < 30%; were awaiting a heart transplant, or had a contraindication to aspirin, clopidogrel, heparin and any other drugs related to this study.

Follow-up and study endpoint

Clinical evaluation was scheduled at 1, 6, and 12 months with annual evaluation up to 5 years. Angiographic and IVUS imaging was obtained at baseline, 6- and 12-month follow-up.

The primary endpoint was in-stent late loss at 6 months. The major secondary endpoint was percent (%) in-stent volume obstruction at 6 months based on IVUS analysis. Other secondary endpoints included the followings: a) in-stent late loss at 1 year; b) in-segment late loss at 6 months and 1 year including proximal and distal evaluations; c) in-stent% volume obstruction at 1 year; d) in-stent and in-segment% diameter stenosis at 6 months and 1 year; e) in-stent and in-segment angiographic binary restenosis (ABR) at 6 months and 1 year; f) persisting incomplete apposition, late incomplete apposition, aneurysm formation, thrombus, persisting dissection at 6 months and 1 year; g) major adverse cardiac events (MACE) rate in-hospital and at 1, 6, 9 months and annually up to 5 years. MACE is comprised of death, myocardial infarction (MI), or clinically driven target lesion revascularization (TLR); g) acute device, procedural and clinical success. All deaths that could not be clearly attributed to another cause were considered a cardiac death. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase MB, in the absence of new Q waves on the surface electrocardiogram.

Quantitative Coronary Angiography evaluation

QCA was performed by means of the CAAS II analysis system (Pie Medical B.V., Maastricht, The Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference diameter, and% diameter stenosis. ABR was defined in every segment as diameter stenosis >50% at follow-up. Late loss was defined as the difference between MLD at post-procedure and MLD at follow-up.

Intravascular Ultrasound Analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased-array IVUS using automated pullback at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program (Curad B.V., Wijk bij Duurstede, The Netherlands) was used for automated 3-D reconstruction of the stented and the peri-stent segments. The lumen, stent boundaries and external elastic membrane were detected using a minimum cost algorithm. The stent volume (SV) and lumen volume (LV) were calculated according to Simpson's rule. The in-stent neointimal volume was calculated as "SV-LV". The % obstruction of the stent volume was calculated as in-stent neointimal volume/stent volume ..100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*[13].

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population. Acute success was analyzed on the safety population. The per-treatment evaluable population consisted of patients who had no bailout and no major protocol deviations. The data for each patient were reviewed in a blinded

manner to determine whether the patient should be included in this analysis population. Analyses based on the per-treatment evaluable population were as "treated". Patients were included in the treatment arm corresponding to the study stent actually received.

The overall sample size calculation for this trial was determined based on the primary endpoint of in-stent late loss at 6 months and on the following assumptions: a single comparison of active to control; one-tailed t-test, unequal and unknown variances in the 2 groups being compared; $\alpha = 0.05$; true mean difference between the control group and the treatment group is 0.48 mm. This assumption was made based on the results of VISION Registry (mean late loss = 0.83 mm)[14], SIRIUS trial (mean late loss = 0.17 mm)[2] and TAXUS IV trial (mean late loss = 0.39 mm)[15]. Assuming the true mean late loss for the treatment group was 0.35 mm, the difference between the control group and treatment group is calculated as: 0.83 mm - 0.35 mm = 0.48 mm. The standard deviation was assumed to be 0.56 mm in the control group and 0.38 mm in the treatment group (based on the results of VISION Registry study and SIRIUS trial with standard deviation for DES adjusted downward from 0.44 mm to 0.38 mm to take into account of 6-month angiography as opposed to 8-month angiography); approximately 20% rate of lost to follow-up or dropout; approximately 10% of patients with bailout stents; given the above assumptions, enrolling 30 patients per arm (analysis of 22 evaluable patients per arm) would have provided 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) provides more than 96% power. Binary variables were compared using Fisher's exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon's rank sum test. Time-to-event variables were compared with Kaplan-Meier analysis and the log rank statistic.

Results

A total of 60 study patients were randomized and consecutively enrolled at 9 investigational sites between December 2003 and April 2004. The safety population is composed of these 60 patients. Of the 60 patients, 3 were excluded from the per-treatment population (1 from the everolimus arm and 2 from the bare stent arm) because of bailout stenting (2) and major protocol deviation (1 patient on a heart transplant waiting list from bare stent arm). Hence the per-treatment population includes 56 patients (27 everolimus arm and 29 control) as illustrated in the trial profile (Figure 1). The control arm and the everolimus arm shared similar demographic characteristics except for patients with hypertension which was significantly higher in the everolimus group than in control (Table 1). Procedural characteristics were explained previously[5].

One-year quantitative coronary angiographic analysis (Table 2)

Nine patients did not have qualifying follow-up angiogram up to 1 year for the following reasons: a) patients withdrew from the clinical trial after the 30-day follow-up visit (1 patient in the everolimus

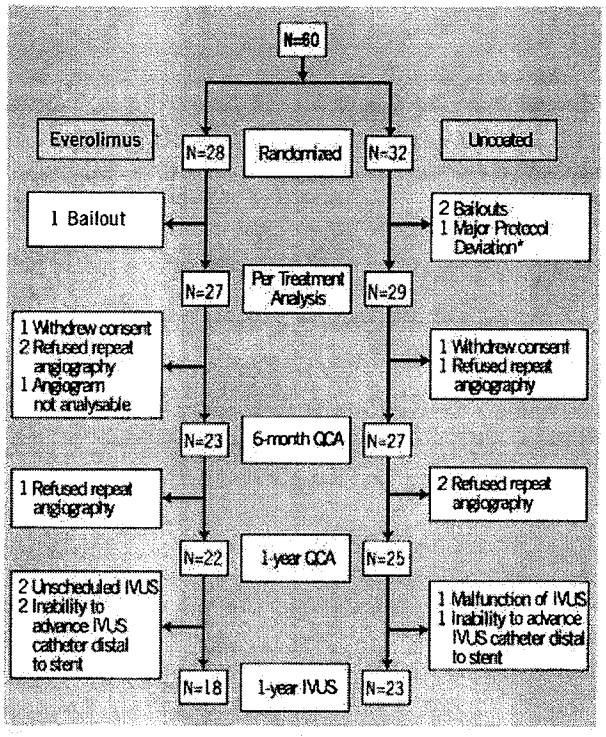

Figure 1. Flowchart of patients. QCA, quantitative coronary angiography; IVUS, intravascular ultrasound.

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

	Everolimus Stent (n = 27)	Uncoated Stent (n = 29)	All Patients (n = 56)
Age(yrs)	64±10	61±9	63±9
Male gender (%)	70	76	73
Current smokers (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring Medication (%)	70	41	55
Hyperlipidemia requiring Medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left Anterior Descending	48	45	46
Left Circumflex	22	21	21
RCA	30	34	32
AHA / ACC# Lesion class (%)			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference vessel diameter (mm±SD)	2.61±0.40	2.71±0.28	2.66±0.34
Lesion length (mm±SD)	10.1±2.6	10.9±3.3	10.5±3.0

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)
# AHA / ACC = American Heart Association / American College of Cardiology.

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Serial analysis)

	Proximal Edge			In Stent			Distal Edge			In Segment Analysis		
	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value
Reference vessel diameter (mm)												
After procedure	2.81±0.36	2.98±0.33	0.27	2.74±0.29	2.80±0.32	0.61	2.70±0.31	2.71±0.32	0.95	2.69±0.33	2.74±0.34	0.81
At 6 months	2.79±0.34	2.64±0.43	0.10	2.74±0.31	2.57±0.39	0.12	2.66±0.37	2.44±0.38	0.06	2.65±0.36	2.58±0.38	0.50
At 1 year	2.75±0.34	2.64±0.39	0.29	2.65±0.32	2.52±0.38	0.22	2.59±0.39	2.40±0.39	0.12	2.59±0.37	2.53±0.38	0.62
Minimal luminal diameter (mm)												
After procedure	2.56±0.44	2.60±0.43	0.93	2.40±0.25	2.42±0.26	0.91	2.29±0.38	2.20±0.45	0.54	2.15±0.32	2.11±0.37	0.56
At 6 months	2.47±0.49	2.15±0.51	0.04	2.28±0.33	1.53±0.40	< 0.001	2.23±0.32	1.99±0.46	0.08	2.07±0.38	1.49±0.39	< 0.001
At 1 year	2.44±0.47	2.12±0.48	0.03	2.16±0.37	1.58±0.44	< 0.001	2.26±0.38	1.96±0.43	0.05	2.01±0.41	1.52±0.42	< 0.001
Late loss (mm)												
At 6 months	0.09±0.19	0.45±0.42	<0.01	0.12±0.22	0.89±0.39	< 0.001	0.06±0.21	0.21±0.41	0.10	0.08±0.20	0.62±0.39	< 0.001
At 1 year	0.12±0.25	0.48±0.39	< 0.001	0.24±0.27	0.84±0.45	< 0.001	0.03±0.25	0.25±0.42	0.04	0.14±0.24	0.59±0.42	< 0.001
Diameter stenosis (%DS)												
After procedure	9±11	13±9	0.53	12±6	13±7	0.36	15±10	19±11	0.22	20±6	23±9	0.18
At 6 months	12±14	18±18	0.17	17±7	41±14	< 0.001	16±8	19±14	0.95	22±11	42±13	< 0.001
At 1 year	11±13	19±15	0.12	18±13	37±17	< 0.001	13±8	18±14	0.24	22±15	40±16	< 0.001

*Patients who underwent angiography at 6 months as well as 1 year.

arm and 1 in the control arm); b) patients refused (3 in the everolimus arm and 3 in the control arm); c) angiogram was not analyzable (1 in the everolimus arm). Serial angiographic follow-up data, which is reported in this paper, were available in 80.4% (45/56) of the per-treatment population, with 74.1% (20/27) in the everolimus arm and 86.2% (25/29) in the control arm (Table 2). The follow-up in-stent MLD was significantly larger in the everolimus arm than in the control arm and the preservation of MLD between 6 months and 1 year was observed (2.28±0.33 mm at 6 months; 2.16±0.37 mm at 1 year) The mean in-stent late loss and% diameter stenosis were 0.24 mm and 18%, respectively, in the everolimus-stent group, as compared with 0.84 mm and 37%, respectively, in the control arm ($p < 0.001$ for each comparison). Figure 2 shows the cumulative frequency of in-stent late loss immediately after the index procedure at 6 months and 1 year in each treatment group. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus-stent group than in the control arm ($p < 0.001$ for proximal and $p = 0.04$ for distal). The in-segment late loss was significantly less in the everolimus arm than in the bare stent arm ($p < 0.001$).

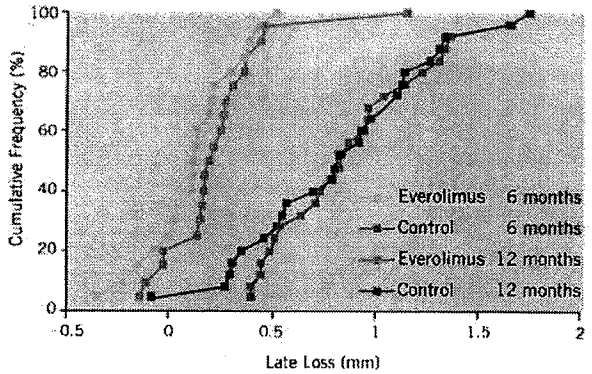

Figure 2. Cumulative frequency of late loss (in-stent) immediately after stenting.

One-year intravascular ultrasound evaluation (Table 3)

In this 1-year report, data in patients who underwent IVUS at 6 months as well as 1 year were presented to identify the volumetric change in serial IVUS examination. Forty-one patients (18 in the everolimus arm; 23 in the control arm) out of 47 patients with 1-year angiography underwent a 1-year IVUS examination. In the remaining

Table 3. Serial IVUS measurements at 1 year follow-up

		Everolimus-Stent (n = 16*)	Uncoated Stent (n = 21*)	P-value
Vessel volume (mm^3)	6 months	296±90	291±74	0.89
	1 year	286±80	290±72	0.82
Stent volume (mm^3)	6 months	137±31	138±31	0.94
	1 year	133±27	137±32	0.79
In-stent neo-intima volume (mm^3)	6 months	9±12	39±20	< 0.001
	1 year	13±9	37±17	< 0.001
Luminal volume (mm^3)	6 months	128±34	98±29	0.03
	1 year	120±30	100±28	0.15
In-stent volume obstruction (%)#	6 months	7±9	29±14	< 0.001
	1 year	10±7	28±12	< 0.001

* Patients who underwent IVUS at 6 months as well as 1 year.
# In-stent volume obstruction = 100*(In-stent neo-intima volume / Stent volume)

6 patients, IVUS was not available: 2 were not properly scheduled for IVUS, 2 inability to advance IVUS catheter distal to stent in the everolimus arm; 1 malfunction of IVUS, 1 inability to advance the IVUS catheter distal to the stent in the control arm. Of the 41 patients, 37 patients (16 in the everolimus arm; 21 in the control arm) had serial IVUS data. Everolimus-eluting stent was associated with a significantly reduced degree of in-stent neointimal hyperplasia as well as in-stent% volume obstruction compared to the bare metal stent (13±9 mm^3 vs. 37±17 mm^3, $p < 0.001$; 10±7% vs. 28±12%, $p < 0.001$), reaching a 64% reduction of the in-stent volume obstruction (Table 3). There was no late acquired or persisting stent malapposion observed either at 6 months or at 1 year.

Major adverse events and clinical outcomes

Table 4 provides results of MACE and target vessel failure for the time points of 1 year. Since the six months follow-up the 1-year results for the everolimus arm included 1 non-Q wave MI due to a spasm during the follow-up IVUS procedure and 2 additional TLRs by PCI. One of these patients had a delayed bailout (TLR) using a non-study drug eluting stent 21 days after the baseline procedure due to a dissection. In the control arm, 1 additional TLR by PCI was observed, this being the patient's 3rd TLR since the index procedure. The hierarchical MACE rate at 1 year was 15.4% for the everolimus arm and 21.4% for the bare stent arm (p=0.59). The MACE rate for the everolimus group increased from 7.7% (2/26) at 6 months to 15.4% (4/26) at 1 year. Three of the 4 overall MACE events in the everolimus group were non-study-device related events. One Q-wave MI was in a non-target vessel, one TLR was due to dissection during the procedure, and one non-Q-wave MI occurred during follow-up IVUS procedure. Total non-hierarchical clinically-driven TLR rates at 1 year were 7.7% in the everolimus arm and 21.4% in the control arm. No adverse effects related to everolimus or the durable polymer were noted. Kaplan-Meier survival estimates were performed for overall MACE (Figure 3). There was no stent thrombosis observed in both arms out to the 1-year time period.

Table 4. Hierarchical Major Adverse Cardiac Events at 1 year in Per-Treatment Population

Event	Everolimus Stent		Uncoated Stent	
	n = 26	%	n = 28	%
Cardiac death	0	0	0	0
Myocardial infarction	2	7.6	0	0
Q-wave	1	3.8	0	0
Non-Q-wave	1	3.8	0	0
Reintervention				
Clinically driven TLR-CABG	0	0	1	3.6
Clinically driven TLR-PCI	2	7.7	5	17.9
Clinically driven TVR-CABG	0	0	0	0
Clinically driven TVR-PCI	0	0	0	0
Target vessel failure	4	15.4	6	21.4
Major adverse cardiac events	4	15.4	6	21.4

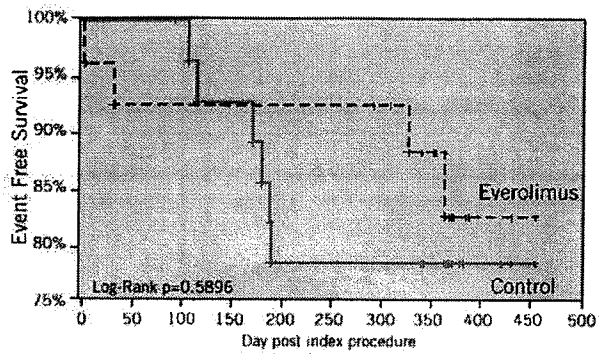

Figure 3. Kaplan-Meier survival curve: MACE. Since the 6-month time point, 1 non-Q wave MI due to a dissection during the follow-up IVUS procedure and 1 clinically-driven additional target lesion revascularization by PCI were observed in everolimus arm. In the control arm, 1 clinically-driven additional target lesion revascularization by PCI was performed.

Discussion

One-year clinical and angiographic follow-up from this trial demonstrates that the polymer-controlled release of everolimus from a coronary stent is safe and effective, with no late adverse effects. The superiority in efficacy, as measured by in-stent late loss, of everolimus-eluting stent as compared to bare stent was sustained at 1 year (71% reduction in late loss). The everolimus arm also maintained its superiority to the bare metal arm in the major secondary IVUS endpoint,% volume obstruction, at 1 year (64% reduction). In addition, the everolimus arm also continued to show significantly lower neointimal volume than the bare stent arm at 1 year (65% reduction).

The current strategy of local drug delivery using sirolimus and paclitaxel is the most promising approach to prevent restenosis, but, at the same time, the strategy has the potential liability for impairing endothelial recovery. Developing new compounds may improve on the potential side effects of the current drug eluting stents, such as delayed healing with re-endothelialization[16] and fibrin[17], early[18] and late stent thrombosis[19]. In this trial, neither stent thrombosis nor other adverse effects related to the drug/durable polymer was observed out to the 1-year time point. On the other hand, an *in vitro* study has shown that sirolimus enhances tissue factor in human endothelial cell[20]. Effect of everolimus on endothelial cell and its similarity or difference compared to sirolimus will have to be investigated. The significant differences between sirolimus- and paclitaxel-eluting stents have recently been reported to likely exist with regard to angiographic as well as clinical outcomes[21,22] "New comers" following these 2 pioneers could be competitors if they can, at least, demonstrate performance as effective as these 2 drug-eluting stents. Studies have suggested that angiographic assessment of late loss is associated with an increased restenosis rate[23,24] as well as a higher risk of TLR[25]. However, it still remains to be determined how to interpret the significance of the slight increase in late loss from 6 months (0.12 mm) to 1 year (0.24 mm) observed in this study stent. Moreover, delayed neointimal growth beyond the first 6 to 9 months has been reported in serial IVUS analyses in some trials

as documented in everolimus-eluting stent (in-stent volume obstruction, 7% at 6 months to 10% at 1 year), which may raise a concern about potential late catch-up phenomenon of DES[26]. Recent head-to-head comparative studies between sirolimus- and paclitaxel-eluting stent are still limited to short-term results[21,22,25,27-30]. Beneficial short-term outcomes do not necessarily translate in long-term efficacy. For example, late catch-up phenomenon has been experienced in vascular brachytherapy[31]. In this respect, the follow-up period of 1 year still seems relatively short to assess the durable safety and efficacy of one drug eluting stent. However, neither sirolimus- nor paclitaxel-eluting stent have been associated with gradually increasing MACE over the years[32,33]. Therefore, we could expect a similar lasting treatment effect of this new eluting stent.

Study limitation

This study with a small patient population provided only safety and efficacy data. Two larger single-blind, randomized controlled studies (The SPIRIT II and SPIRIT III) further evaluating this study stent compared to the paclitaxel-eluting stent for the treatment of coronary artery disease are under way.

Conclusions

At 1 year, this trial demonstrated that the treatment effect observed at 6 months was sustained at 1 year for everolimus-eluting stent. The in-stent and in-segment late loss in the everolimus arm was reduced by 71% and 78% compared to those in the bare metal arm, respectively. These observations were consistent with IVUS measurements. The 1-year results showed a reduction of neointimal volume by 65% as compared to bare metal stent. A small increase in % volume obstruction in event-free patients was observed from 6 to 12 months, but is considered clinically insignificant. Both the angiographic and IVUS measurements showed that the patency of the target vessel treated with everolimus-eluting stent was maintained at 1 year.

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UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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THURSDAY,
NOVEMBER 29, 2007

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The meeting convened at 8:00 a.m. at the Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, CLYDE W. YANCY, M.D., Acting Panel Chairperson, presiding.

PANEL MEMBERS PRESENT:

CLYDE YANCY, M.D, Acting Chairperson
RICHARD L. PAGE, M.D., Voting Member
JOHN C. SOMBERG, M.D., Voting Member
EUGENE H. BLACKSTONE, M.D., Consultant
JEFFREY A. BRINKER, M.D., Consultant
JOHN W. HIRSHFELD, M.D., Consultant
VALLUVAN JEEVANANDAM, M.D., Consultant
NORMAN S. KATO, M.D., Consultant
WARREN K. LASKEY, M.D., Consultant
DOUGLAS MORRISON, M.D., Consultant
SHARON-LISE NORMAND, Ph.D., Consultant
MARCIA S. YAROSS, Ph.D., Industry Representative
KAREN R. RUE, Consumer Representative

looking at the percentage of tissue growth now on a volumetric basis within the stent margins that were occluding the illumene, if you will.

You can see that, similarly, there was a marked reduction in the percent volume obstruction from almost 30 percent of the stent being filled with tissue with the VISION bare metal stent. And this was reduced 72 percent to an 8 percent volume obstruction with the XIENCE V stent, again highly statistically significant.

Now, I did mention that this trial was underpowered for clinical events, but, of course, these patients were followed clinically. And we have data now out to three years on the patients that were enrolled in the XIENCE V stent versus the VISION stent in SPIRIT FIRST.

You can see that, importantly, there were no cardiac deaths in either arm. Other events were relatively low in frequency, especially in the XIENCE V arm, in these

patients followed out to three years.

I will point out that there were trends towards reduced target lesion revascularization. This is the purest clinical surrogate of drug-eluting stent efficacy. This means ischemia leading to a repeat procedure due to restenosis, either at the lesion itself or at the margins out five millimeters from the lesion; the composite endpoints of major adverse cardiovascular events, which I will describe further later; and target vessel failure, also tended to be reduced with the XIENCE V stent, but, again, we weren't powered to show differences for this trial. And, perhaps most importantly, there were no cases of stent thrombosis out to three years in this small study with either the XIENCE V stent or the VISION bare metal stent.

So the conclusions from the SPIRIT FIRST trial were that this trial met both its pre-specified primary and major secondary

endpoints, demonstrating superiority of the XIENCE V stent compared to the bare metal multi-link VISION stent in reducing late loss and percent volume obstruction.

We now entered a phase in clinical development where most physicians were using drug-eluting stents for the majority of patients with coronary artery disease. And it no longer became feasible to compare drug-eluting stents to bare metal stents.

So now we will be looking at studies comparing the XIENCE V stent to the otherwise widely utilized paclitaxel-eluting TAXUS stent. So this is DES versus DES. And the first such study, which was designed in Europe, was the SPIRIT II randomized controlled trial.

This was a more challenging study in which high-risk patients were enrolled. Patients were enrolled with up to two de novo lesions, rather than one, with a maximum of one lesion per epicardial vessel. And the

You can see here that there tends to be less target vessel failure in the XIENCE V arm compared to the TAXUS arm, 11.1 percent versus 8.5 percent, a relative 25 percent difference, but the p-value is .8. But this trend -- and I will get back to this -- is due to what tends to be less peri-procedural non-Q-wave myocardial infarctions very early on, with then what tends to be a little bit less ischemic target lesion revascularization later on.

This comes out, actually, more so when one now looks at the more stent-specific composite endpoint of major adverse cardiovascular events. Again, this is cardiac death, myocardial infarction, or target lesion revascularization that is right at the site of the stent and at the edges of the stent.

Here you can see the difference again in peri-procedural non-Q-wave MIs. And then you do see the curve spread over time, as I will show you later, because of less target

lesion revascularization with XIENCE V stent such that at the end of one year, we actually see, just like we saw in SPIRIT II, a significant 43 percent reduction in major adverse cardiovascular events with one drug-eluting stent versus the other TAXUS stent. So 5.9 percent with XIENCE V, 10.2 percent with TAXUS. And this is a fairly striking 43 percent reduction.

So here are all the one-year result endpoint event rates. One can see again stent thrombosis, both per-protocol and by the ARC definitions, infrequent in both groups and no different; cardiac death, also infrequent in both groups and not different; overall myocardial infarctions out to one year, somewhat catch up.

And you can see 2.8 percent with XIENCE V, 4.1 percent with TAXUS. Target lesion revascularization in this trial, of course, very underpowered for this endpoint, tended to be numerically less with XIENCE V

compared to TAXUS, so overall major adverse cardiovascular events.

And this is now using binomial numbers, slightly different than what I showed you at the hazard curves. This is a relative risk but a 42 percent reduction confidence interval, .37 to .90, 10.3 percent with TAXUS reduced to 6 percent with XIENCE.

This trial, with more complex lesions and patients, actually had a significantly higher rate of the noise, if you will, additional revascularizations outside the target lesion but similar between the two stents, as one would expect. And, therefore, when one looks at TVF, it somewhat dilutes the ability to see differences compared to MACE. Nonetheless, you see this numerical trend, not statistically significant for a 24 percent reduction in TVF with XIENCE compared to TAXUS.

Thus, the conclusions from SPIRIT III was that the pivotal United States-based

myocardial infarctions from 2.9 percent with the TAXUS stent versus one percent with the XIENCE V stent, a 66 percent reduction. Thus, the composite endpoint of cardiac death or MI, of course, had the exact same numbers since there were no cardiac deaths.

Now, we don't expect many TLRs at 30 days with any sort of stent, and there weren't many, similar with the 2 stents. Thus, both major adverse cardiovascular events and target vessel failure were actually improved at 30 days with the XIENCE V stent compared to the TAXUS stent.

Now, we don't know in detail why this was, but, actually, this is not surprising. I was actually the first one to point out that in TAXUS V, we do have a higher rate of peri-procedural myocardial infarctions with the larger strut stent that we had tested in that study. And presumably it's the thinner stet strut and the more adhesive polymer that has less bonding, webbing, et

cetera, that is potentially less thrombogenic that leads to less side-branch compromise and perhaps other events that leads to an enhanced safety profile at 30 days.

Now, these are not only small, tiny myocardial infarctions. When we look at the level of the myocardial infarction as estimated by the peak CPK less than five, which we could consider small MIs, versus five to ten, which you might consider moderate sized MIs, versus greater than ten times the upper limits of normal, which are large MIs and nobody would argue are prognostically important, you can see that the XIENCE V stent compared to the TAXUS stent tends to reduce the levels of all sorts of MI, small, moderate, and large.

Now if we go to the one-year outcomes in these trials, first, I will show you the lower-frequency safety events. This is stent thrombosis with a pre-specified protocol definition. And one can see almost

identical rates of stent thrombosis out to one year with these two devices: 0.8 percent with TAXUS, 0.7 percent with XIENCE.

When we used the ARC definite or probable definitions, again, this is what most people are using right now, you can see that, again, out at one year, there is no difference in stent thrombosis between the 2 devices: 0.8 percent with TAXUS and with XIENCE V.

If we look at all-cause death at one year, all-cause death is infrequent. And there is no difference in all-cause death, 1.8 percent with TAXUS and 1.3 percent with XIENCE. What you are going to see in all of the next series of slides is that while these low-frequency safety events tend not to be different, you will see that they do tend to benefit or favor the XIENCE V stent, at least in terms of lower numerical rates of adverse events, which is reassuring.

So if we look at cardiac death at one year, one percent with TAXUS, zero percent

with XIENCE V, of course, low frequency, still not statistically significant but reassuring, when we look at MIs, I showed you that the 30-day MI rates were statistically significant.

And the curves stay roughly parallel since that time, so overall MIs out to one year, 4 percent with TAXUS, 2.3 percent with XIENCE, a relative 44 percent reduction with a borderline p-value of 0.08.

Thus, looking at our pre-specified endpoint of cardiac death or myocardial infarction at one year, again, you can see that it tends to favor the XIENCE V stent, 2.7 percent versus 4.5 percent with TAXUS, a relative 40 percent reduction, but the p-value is .10.

Now, if we look at efficacy measures, this is where it starts to also become revealing because we actually do see a statistically significant reduction in target lesion revascularization or clinical